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Monitoring activated clotting time for combined heparin and aprotinin application: in vivo evaluation of a new aprotinin-insensitive test using Sonoclot☆

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Abstract

Objective: Kaolin-based activated clotting time assessed by HEMOCHRON (HkACT) is a clinical standard for heparin monitoring alone and combined with aprotinin during cardiopulmonary bypass (CPB). However, aprotinin is known to prolong not only celite-based but also kaolin-based activated clotting time. Overestimation of activated clotting times implies a potential hazardous risk of subtherapeutic heparin anticoagulation. Recently, a novel 'aprotinin-insensitive' activated clotting time test has been developed for the SONOCLOT analyzer (SaiACT). The aim of our study was to evaluate SaiACT in patients undergoing CPB in presence of heparin and aprotinin. **Methods:** Blood samples were taken from 44 elective cardiac surgery patients at the following measurement time points: baseline (T0); before CPB after heparinization (T1 and T2); on CPB, before administration of aprotinin (T3); 15, 30, and 60 min on CPB after administration of aprotinin (T4, T5, and T6); after protamine infusion (T7). On each measurement time point, activated clotting time was assessed with HkACT and SaiACT, both in duplicate. Furthermore, the rate of factor Xa inhibition and antithrombin concentration were measured. Statistical analysis was done using Bland and Altman analysis, Pearson's correlation, and ANOVA with post hoc Bonferroni–Dunn correction. **Results:** Monitoring anticoagulation with SaiACT showed reliable readings. Compared to the established HkACT, SaiACT values were lower at all measurement time points. On CPB but before administration of aprotinin (T3), SaiACT values (mean ± SD) were 44 ± 118 s lower compared to HkACT. However, the difference between the two measurement techniques increased significantly on CPB after aprotinin administration (T4–T6; 89 ± 152 s, $P = 0.032$). Correlation of ACT measurements with anti-Xa activity was unchanged for SaiACT before and after aprotinin administration ($r^2 = 0.473$ and 0.487, respectively; $P = 0.794$), but was lower for HkACT after aprotinin administration ($r^2 = 0.481$ and 0.361, respectively; $P = 0.041$). On CPB after administration of aprotinin, 96% of all ACT values were classified as therapeutic by HkACT, but only 86% of all values were classified therapeutic if ACT was determined by SaiACT. Test variability was comparable for SaiACT and HkACT. **Conclusions:** The use of SaiACT may result in more consistent heparin management that is less affected by aprotinin and a corresponding increase in heparin administration for patients receiving aprotinin.

Keywords: Activated clotting time (ACT); Aprotinin; Kaolin; Anticoagulation; Measurement techniques; Coagulation; Cardiopulmonary bypass

1. Introduction

Aprotinin has been shown to reduce postoperative bleeding in patients after cardiopulmonary bypass (CPB) [1]. Measurement of activated clotting time (ACT) is a standard monitoring procedure for guiding heparin-induced anticoagulation. Depending on the coagulation activator used, ACT measurements may be prolonged to various degrees in the presence of aprotinin. Overestimation of activated clotting times implies a potential hazardous risk of subtherapeutic heparin anticoagulation and must be avoided. When routine doses of heparin and aprotinin are applied for CPB, kaolin-based ACT is considered to be a standard test to guide heparin management because kaolin-based ACT is less affected than celite-based ACT [2,3]. However, kaolin-based ACT has also been shown to be prolonged significantly in the presence of aprotinin [3,4].

Recently, a new ACT test, SaiACT (Sonoclot® Coagulation & Platelet Function Analyzer, Sienco Inc., Arvada, CO, USA), has been developed for the SONOCLOT analyzer, with specific

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claims to provide a heparin dose response substantially unaffected by the presence of aprotinin. This novel test is labeled 'aprotinin-insensitive' by the manufacturer (SONOCLOT's aprotinin-insensitive ACT, SaiACT). The cuvette is manufactured with a blend of celite to initiate blood coagulation and a type of clay to neutralize aprotinin. Like other ACT machines, the SONOCLOT analyzer also incorporates a mechanical means to detect a fibrin clot. A resonant mechanical oscillator responds to viscoelastic changes that occur during clot formation. After adding a blood sample to the SaiACT cuvette and mixing the sample with the mineral reagents, the change in impedance to movement imposed by the developing clot is measured and an activated clotting time determined.

We have previously evaluated this new SaiACT technology in vitro in presence of clinically relevant concentrations of heparin, aprotinin, and hemodilution [5]. Addition of aprotinin to heparinized blood samples induced no significant changes of SaiACT measurements. By contrast, ACT values measured with an established kaolin-based ACT from HEMOCHRON (HkACT; Hemochron® 801, International Technidyne Corp., Edison, NJ, USA) increased significantly in heparinized samples if aprotinin was present, and in vitro hemodilution pronounced this effect.

The aim of the present study was to evaluate this new SaiACT from SONOCLOT in vivo in patients undergoing CPB in the presence of heparin and aprotinin, and to compare the SaiACT test with an established kaolin-based ACT from HEMOCHRON (HkACT) as well as plasma levels of heparin measured by anti-factor Xa activity (anti-Xa).

2. Materials and methods

With local ethics committee approval and patient-written informed consent, 44 patients scheduled for elective cardiac surgery with CPB were enrolled. Inclusion criteria were age >18 years and one of the following surgical procedures: aortic valve replacement (AVR), aortic aneurysm repair, mitral valve surgery (MVS, reconstruction or replacement), and complex procedures involving combined valve coronary artery bypass grafting (CABG) or multiple valve procedures. At our hospital, most CABG procedures are done without CPB (i.e., off-pump technique); hence, these patients were not available for inclusion in this study. Exclusion criteria were repair of congenital heart defects, emergency procedures and known coagulation disorders (including pharmacologically induced coagulopathies, i.e., pre-treatment with any anticoagulants or anti-platelet drug).

Anesthesia, heparin anticoagulation, CPB, protamine reversal, and transfusion therapy were all managed by standardized institutional protocols. Anesthesia was induced and maintained with propofol and fentanyl, and pancuronium bromide was given for neuromuscular blockade. Fluid management was done with lactated Ringer's solution (Laboratory Dr. Bichsel AG, Switzerland) and 6% hydroxy ethyl starch solution (HES 130/0.4, Voluven®, Fresenius Kabi, Bad Homburg, Germany). Anticoagulation for CPB was attained with IV porcine heparin (Liquemin®, Roche Pharma, Switzerland) 300 U kg^{-1}. Heparin management was guided by HkACT, and HkACT > 480 s was accepted as adequate anticoagulation for CPB. CPB was performed with a membrane oxygenator (Quadrox HMO1010, Maquet Cardiopulmonary AG, Hirlingen, Germany) under moderate hypothermia (28–32 °C) at flows between 2.2 and 2.4 l min^{-1} m^{-2}. Ten thousand units of heparin but no aprotinin was added to the standard priming volume (1800 ml) of the CPB circuit. After initiating the CPB, one bolus of aprotinin 2 Mio kIU (Trasylol®; Bayer Pharmaceuticals Corp., Germany) was administered directly to the CPB circuit (modified low-dose aprotinin regimen, also called pump-prime-only regimen [6]). To keep HkACT > 480 s, additional heparin in 5000 U increments were administered during CPB, if necessary. Anticoagulation was reversed after rewarming and separation from CPB with protamine up to a maximum dose of 1 mg per 100 U of total heparin dose administered.

Blood samples were taken from an unheparinized central venous line after removing five dead space volumes of blood at the following measurement time points: baseline, after induction of anesthesia but before skin incision (T0); before CPB, 3 min after the first (200 U kg^{-1}, T1) and 3 min after the second dose (100 U kg^{-1}, T2) of heparin; 5 min on CPB, before administration of aprotinin 2 Mio kIU to the CBP circuit (T3); 15, 30, and 60 min on CPB after administration of aprotinin (T4, T5, and T6); and after protamine infusion and re-transfusion of the remaining blood from the CPB circuit (T7).

ACT was measured with two different ACT analyzers each in duplicate, the SONOCLOT analyzer with the novel 'aprotinin-insensitive' ACT test (SaiACT; Sonoclot® Coagulation & Platelet Function Analyzer, Sienco Inc.; normal range in whole blood 62–93 s) and the HEMOCHRON analyzer with the standard kaolin-based ACT test (HkACT; Hemochron® 801, International Technidyne Corp.; normal range in whole blood 91–151 s). For the SaiACT, 360 μl of freshly withdrawn blood was filled into the cuvette, mixed and analyzed. Immediately after, 2 ml of the same blood specimen was filled into a HkACT cuvette, mixed and analyzed. The performance of each machine was verified with recommended quality control tests according to the manufacturers. Results were recorded as mean of duplicate measurements for each of the devices. All measurements were performed by the same investigator to avoid inter-observer variability.

To measure laboratory blood coagulation, further blood samples were withdrawn at each time point in citrated tubes (final concentration of sodium citrate 0.109 mol l^{-1}; Vacuette® 9NC, Greiner Bio-One, Austria). The samples were immediately centrifuged (2500 × *g* for 20 min at 4 °C), and the supernatant (plasma) stored at −32 °C for later measurements. Blood coagulation parameters were measured on an automated STA-R® coagulation analyzer (Diagnostica Stago, Asnière, France). At each time point, the rate of factor Xa inhibition (anti-Xa, assessment of the heparin concentration) and antithrombin concentration (AT) was measured. Anti-Xa activity was determined by assessing the level of inhibition of the hydrolysis of a chromogenic substrate (by the factor Xa) in the presence of heparin-antithrombin complexes with the STA®-Rotachrom-Heparin test (Diagnostica Stago). This assay is specifically designed to reflect a directly proportional relationship between the rate of factor Xa inhibition and the heparin concentration. Some

of the samples had to be diluted with normal pooled plasma prior to the analysis, in order to be on the linear part of the standard curve (0.10–0.70 U ml^{-1}). AT activity was determined with the use of the chromogenic STA®-Antithrombin-III test (Diagnostica Stago, normal range in whole blood = 80–120%). All coagulation tests and quality controls (on normal and abnormal levels) were performed according to the manufacturer's instructions.

Statistical analysis was done using StatView® for Windows version 5.01® (SAS Institute Inc., Cary, NC, USA) and SPSS for Windows Release 12.0.2 (SPSS Inc., Chicago, IL, USA). Bland and Altman analysis was done to compare SaiACT with HkACT [7]. Bias is defined as mean of difference (SaiACT − HkACT) and ±2 standard deviations (SD) reflect upper and lower limits of agreement. ANOVA for repeated measures with post hoc Bonferroni–Dunn correction and a two-sided paired Student's *t*-test were performed to compare the coagulation parameters at different time points. Pearson's correlations with Fisher's z-transformation and Hotelling Williams' test were used to assess the relationship between both SaiACT and HkACT with heparin levels (anti-Xa) before and after aprotinin administration as well as between AT and hematocrit. Test variability of duplicate measurements was calculated as percentage of the mean of duplicate measurements. Unless otherwise stated, data are presented as mean ± SD. *P*-values <0.05 were considered statistically significant.

3. Results

A total of 333 blood samples from 44 patients were studied. For 19 patients (43%) CPB time was 60–80 min and thus, ACT measurements for the last measurement on CPB (T6) were not performed. Demographic data, procedures, and intraoperative data are summarized in Table 1. ACT measurements were done in duplicates with SaiACT (*n* = 666) and HkACT (*n* = 666) in a wide range before, during, and after CPB (Fig. 1A). Both ACT analyzers were user friendly and no technical or handling problems occurred with either device during the study period.

Table 1
Demographic data, procedures, and intraoperative data

Demographic data	
Age, years	65 ± 13
Sex, M/F	*n* = 25 (57%)/*n* = 19 (43%)
Euro Score	6.1 ± 2.6
Procedures (*n*)	
AVR	10 (23%)
AVR+	22 (50%)
MVR	8 (18%)
MVR+	4 (9%)
OP time, min	223 ± 65
CPB time, min	108 ± 31
ACC time, min	67 ± 21

Data are presented as mean ± SD. AVR, aortic valve replacement; AVR+, AVR + coronary artery bypass graft surgery (*n* = 9), resection of a subaortic stenosis (*n* = 6), size reduction ascending aortoplasty (*n* = 4), or composite graft (*n* = 3); MVR, mitral valve replacement/reconstruction; MVR+, MVR + coronary artery bypass graft surgery; OP, operation; CPB, cardiopulmonary bypass, ACC, aortic cross clamping.

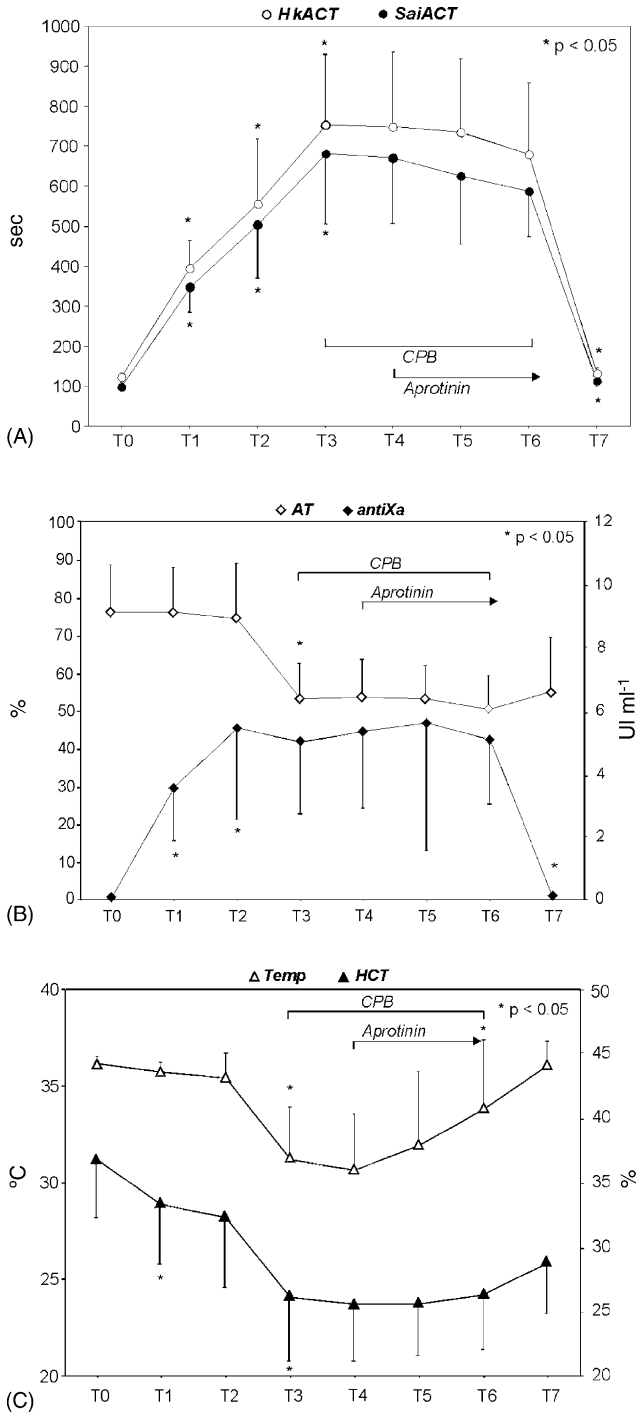

Fig. 1. Time course of SONOCLOT's aprotinin-insensitive ACT (SaiACT) and HEMOCHRON's kaolin-based ACT (HkACT) (A), rate of factor Xa inhibition (anti-Xa) and antithrombin (AT) concentration (B), and hematocrit and temperature (C). At each time point, 44 blood samples were measured by both ACT analyzers with the exception of T6 (25 blood samples). Values are presented as mean ± SD. The measurement time points were: baseline, after induction of anesthesia but before skin incision (T0); before CPB, 3 min after 1st (200 U kg^{-1}, T1) and 3 min after second dose of heparin (100 U kg^{-1}, T2); 5 min on CPB, before administration of aprotinin 2 Mio kIU to the CBP circuit (T3); 15, 30, and 60 min on CPB, after administration of aprotinin (T4, T5, and T6); after protamine infusion (T7).

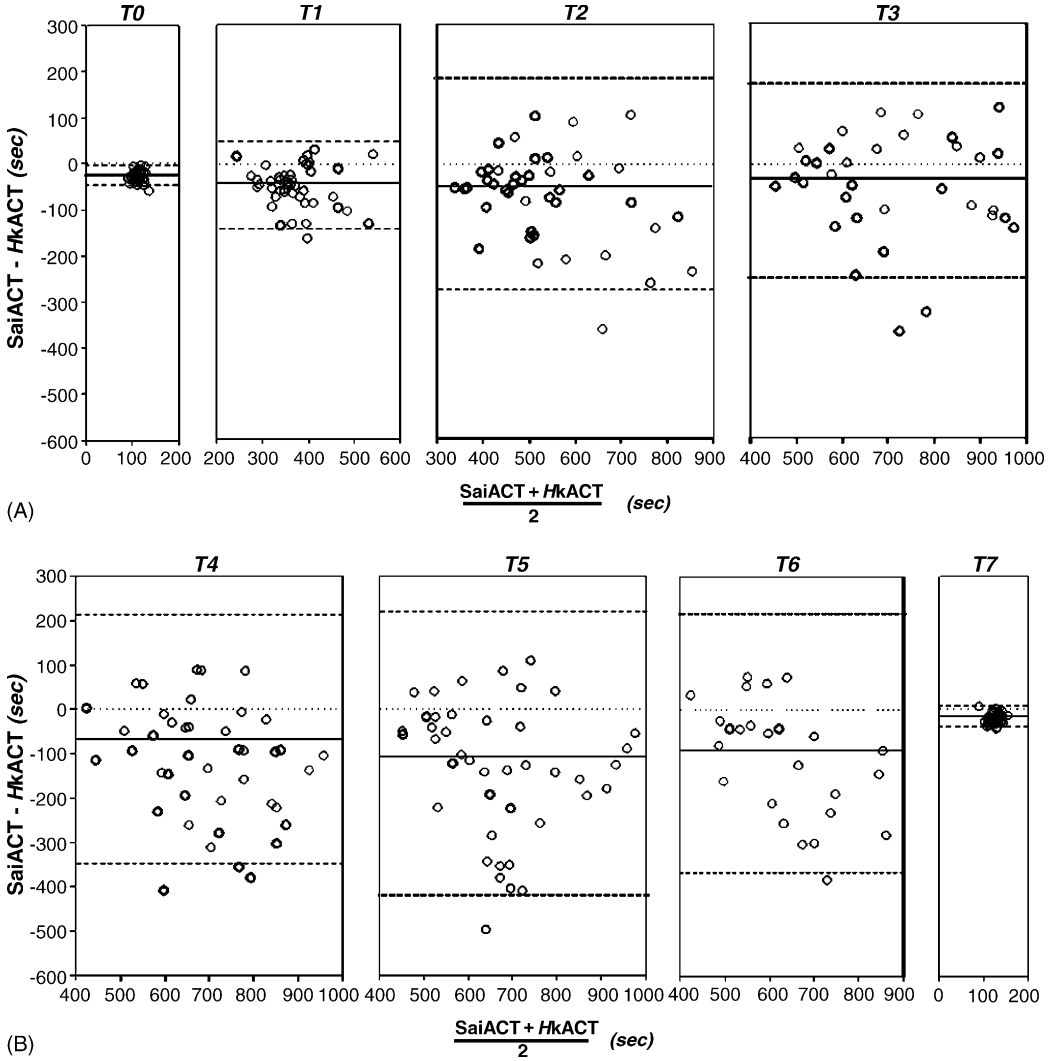

Fig. 2. Bland and Altman analysis between SONOCLOT's aprotinin-insensitive ACT (SaiACT) and HEMOCHRON's kaolin-based ACT (HkACT) before (T0–T3; A) and after administration of aprotinin (T4–T7; B). Bias (black line) is defined as mean of difference (SaiACT − HkACT) and ±2 standard deviations (SD) reflect upper and lower limits of agreement (broken lines). For further details on measurement time points see Fig. 1 or Section 2. Mean bias ± SD: T0 = −26 ± 11 s, T1 = −46 ± 50 s, T2 = −55 ± 124 s, T3 = −44 ± 118 s, T4 = −72 ± 144 s, T5 = −102 ± 165 s, T6 = −93 ± 147 s, T7 = −18 ± 11 s.

Baseline values (T0) and values after protamine administration (T7) were 19–26% lower for SaiACT compared to HkACT ($P < 0.001$, Fig. 2). Anticoagulation with heparin (T1 and T2) resulted in a significant, comparable increase of SaiACT, HkACT, and anti-Xa activity (Fig. 1A and B). Initiating CPB (hemodilution, T3) further increased SaiACT and HkACT, but anti-Xa remained unchanged (10,000 U heparin was added to the priming volume of the CPB circuit). AT, hematocrit, and body temperature decreased significantly (Fig. 1B and C). Administration of aprotinin increased the bias between SaiACT and HkACT during CPB significantly (Figs. 1A and 2; T4–T6), whereas anti-Xa and AT remained unchanged (Fig. 1B). There was some correlation between AT and hematocrit throughout the study period ($r^2 = 0.289$, $P < 0.001$).

Bias between SaiACT and HkACT at each measurement time point is shown in Fig. 2A (before aprotinin administration, T0–T3) and Fig. 2B (after aprotinin administration, T4–T7). Overall bias before administration of aprotinin (T0–T3) was −48 ± 101 s and increased significantly after infusion of aprotinin (T4–T7) to −91 ± 151 s ($P = 0.032$). Correlation for SaiACT and HkACT was better before (T0–T3; $r^2 = 0.880$) than after aprotinin administration (T4–T6; $r^2 = 0.801$, $P < 0.001$).

Correlation of ACT measurements with anti-Xa activity (Table 2) was comparable for SaiACT and HkACT before patients received aprotinin (T0–T3). After administration of

Table 2
Pearson's correlation coefficients (r^2) comparing SONOCLOT's aprotinin-insensitive ACT (SaiACT) and HEMOCHRON's kaolin-based ACT (HkACT) with rate of factor Xa inhibition (anti-Xa) before and after administration of aprotinin

		SaiACT	HkACT
Before aprotinin (T0–T3)	anti-Xa	0.473 ($P < 0.001$)	0.481 ($P < 0.001$)
After aprotinin (T4–T7)	anti-Xa	0.497 ($P < 0.001$)	0.361 ($P < 0.001$)
r^2 before versus r^2 after aprotinin		$P = 0.799$	$P = 0.041$

aprotinin (T4–T7), correlation remained unchanged for SaiACT, but worsened significantly for HkACT.

Dividing measured ACT values in two groups – below and above the therapeutic ACT target of 480 s for a safe CPB procedure – the following results were obtained: On CPB after administration of aprotinin (T4–T6), 96% of all values were classified as therapeutic by HkACT, but this was only the case in 86% of all values if ACT was determined by SaiACT. Twenty-five percent of all studied patients experienced at least one episode with 'therapeutic' ACT values (>480 s) determined by HkACT but 'inadequate' ACT values (<480 s) when determined by SaiACT.

Test variability was comparable for both ACT measurement techniques: Overall test variability for SaiACT was $7.5 \pm 7.4\%$ and for HkACT $7.8 \pm 11\%$. No significant difference was observed in heparinized blood samples before (T1–T3) and after (T4–T7) aprotinin administration (SaiACT: $P = 0.438$; HkACT: $P = 0.087$).

4. Discussion

The novel 'aprotinin-insensitive' ACT from SONOCLOT (SaiACT) showed lower readings at all measurement time points in patients undergoing CPB before and after administration of aprotinin when compared to the kaolin-based ACT from HEMOCHRON (HkACT). Bias between the two measurement techniques increased significantly after aprotinin administration. Correlation of ACT measurements with anti-Xa activity was unchanged for SaiACT before and after aprotinin administration, but declined significantly for HkACT measurements after aprotinin administration. On CPB after administration of aprotinin, 96% of all ACT values were classified as therapeutic by HkACT, but this was only the case in 86% of all values if ACT was determined by SaiACT.

Heparin anticoagulation is used during cardiac surgery to prevent overt thrombosis of the extracorporeal circuit and to minimize excessive CPB-related activation of the hemostatic system. As there is substantial variability of heparin anticoagulant responsiveness, heparin administration is usually monitored by point-of-care instruments that measure ACT. The ACT, initially described as a manual technique by Hattersley [8] and introduced into cardiac surgery by Bull et al. [9] is the amount of time it takes to form a clot by contact activation of the coagulation cascade. ACT measurement may be performed using different coagulation activators like diatomaceous earth (celite), clay (kaolin), glass-beads, or a blend of these materials. Different activators have different characteristics and interactions, and even the same coagulation activator manufactured by different companies respond differently under similar conditions [3]. Results from different ACT tests cannot be used interchangeably. Different baseline for SaiACT has to be accounted for when used as alternative to HkACT. In this study, baseline SaiACT values were 19–26% lower compared to HkACT, on average. This finding has to be considered using SaiACT to guide anticoagulation during CPB.

Although widely used, many factors – patient, operator, and equipment – may affect ACT measurements. The ACT is subject to bias from various interventions that are typical during cardiac surgery, particularly patient hypothermia [10], inadequacy of specimen warming [11], hemodilution [11], quantitative and qualitative platelet abnormalities [12], or aprotinin infusion [2,3]. The technique has been criticized because of its extreme variability and the weak correlation with plasma heparin concentrations during CPB [13]. Our data show a strong correlation between ACT measurements and heparin concentration before CPB. Initiating CPB increased both ACT readings similarly but heparin levels remained unchanged (Fig. 1A and B) worsening the correlation between ACT measurements and anti-Xa. Hemodilution by itself has been shown to be responsible for the prolongation of the ACT measurements during initiating CPB [11]. Furthermore, correlation of ACT measurements with anti-Xa activity was unchanged for SaiACT before and after aprotinin administration, but declined significantly for HkACT measurements after aprotinin administration.

The concentration of AT paralleled the course of the hematocrit therefore reflecting at least in part the degree of hemodilution by the CPB, as shown by Linden et al. [14] earlier. Interestingly, despite the decrease in AT to about 50% after initiating CPB in our study, the concentration of AT was still adequate for heparin to exert its potent anticoagulant effect. It is known that AT concentrations correlate with heparin's effect to inhibit coagulation: lower AT levels are associated with a decreased heparin dose response as measured by the ACT. However, in vitro data showed that only AT levels <30% are associated with impaired heparin action [15].

Aprotinin has been questioned lately for its overall safety in two large studies on patients undergoing CPB: Mangano et al. [16] and Karkouti et al. [17] reported dose-dependent serious renal, cardio- and cerebrovascular adverse events after aprotinin administration in this clinical setting. Interestingly, patients treated with aminocaproic acid or tranexamic acid showed similar reduction in blood loss compared to patients treated with aprotinin, but these patients had no renal, cardio- and cerebrovascular adverse events [16,17]. The question remains, why only aprotinin but not the other antifibrinolytic agents caused these serious adverse events. In both studies, patients received one of the anti-fibrinolytic agents at physician discretion, i.e., the studies were non-randomized. However, both studies included large numbers of patients and statistical procedures were used to adjust for known differences between the treatment groups. Another possible explanation for the adverse events seen in patients treated with aprotinin could have been that these patients were under-heparinized during CPB. Aprotinin is a non-specific serine protease inhibitor and may prolong ACT measurements to various degrees depending on the coagulation activator used. This drug is known to inhibit contact activation, preferentially celite mediated activation in vitro [18,19]. Kaolin-based ACT is less affected than celite-based ACT, most likely because kaolin binds aprotinin [20] and because kaolin more potently activates coagulation than celite [18]. However, kaolin-based ACT has also been shown to be prolonged significantly in the presence of aprotinin [3,4]. Overestimation of anticoagulation, i.e., falsely prolonged ACT implies a potential hazardous risk of subtherapeutic heparin anticoagulation and must be avoided during CPB. For example, in a recent investigation, Koster

et al. [21] showed that heparin management with kaolin-based ACT resulted in lower heparin concentrations compared to a heparin concentration-based anticoagulation management during CPB. These lower heparin concentrations used in patients managed by kaolin-based ACTs were associated with increased hemostatic activation and inflammatory response.

Limited data exist that define the optimal ACT for initiation and maintenance of CPB. In a recent survey of the Society of Cardiovascular Anesthesiology and American Society of Extracorporeal Circulation, it was found that the target ACT used by 82% of responders was 400—480 s or greater, with an additional 4.5% targeting an even higher ACT [10]. When the achievement of the usual target of >480 s was considered, an adequate anticoagulation during CPB after aprotinin administration, 96% of all ACT values were classified as therapeutic by HkACT, but this was only the case in 86% of all values if ACT was determined by SaiACT.

Each ACT measurement was performed in duplicate for both SaiACT and HkACT to evaluate test variability. Both methods were comparable and showed mean test variability between 7 and 8%. According to the manufacturers of both analyzers, coefficient of variation should not exceed 5% under control conditions. Nonetheless, published data on performance of ACT devices in control plasma and whole blood differ largely and were mostly below 10% [22,23].

Costs for the two ACT tests used in this study are comparable at our institution: we pay approximately three EUR for both ACT tests taking into account our current workload (we perform 7000—10,000 ACT tests per year) and rental agreements.

This study has some limitations. We were able to conclude that heparin management with SaiACT may result in an increased administration of heparin. However, we did not answer the question if higher heparin doses in patients treated with aprotinin are justified in terms of patient's outcomes. Further studies are needed, measuring coagulation activation as well as recording patient's outcome data in heparinized patients on CPB guided by SaiACT. Furthermore, according to our institutional protocol, our patients received aprotinin only in a modified half-dose regimen (pump-prime-only regimen, 2 Mio kIU in CPB circuit). For this regimen, anticipated aprotinin serum concentrations range between 150 and 250 kIU ml^{-1} [24]. Additionally, different volumes of blood used to measure ACT with the SONOCLOT (360 μl) and the HEMOCHRON analyzer (2 ml) have to be considered. Both measurements may be affected to a varying degree by external conditions: Large volume ACT tests may be more influenced by temperature and the hypocoagulability seen in hemodiluted blood samples may depend on the sampling volume used [25].

In conclusion, the novel 'aprotinin-insensitive' ACT test measured by the SONOCLOT analyzer (SaiACT) may be a valuable alternative to monitor heparin anticoagulation in presence of aprotinin compared to the kaolin-based ACT assessed by HEMOCHRON (HkACT). Values for SaiACT are lower than values for HkACT, and administration of aprotinin increases this difference significantly. Therefore, the use of SaiACT may result in an increased administration of heparin.

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